

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number  
**WO 2004/091580 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 9/16**, 9/50

Opp. Naval depot, Ghatkopar (West), Bombay 400 986, Maharashtra State (IN).

(21) International Application Number:  
PCT/EP2004/003255

(74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(22) International Filing Date: 26 March 2004 (26.03.2004)

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0307277.4 28 March 2003 (28.03.2003) GB  
0316087.6 9 July 2003 (09.07.2003) GB

(71) Applicant (*for all designated States except US*): **SANDOZ AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DOSHI, Chetan** [IN/IN]; C-3, 403, Veenasagar, Co-Operative Housing Society, Lal Bahadur Shastri Marg, Mulund (West) 400 080, Mumbai (IN). **GOPINATHAN, Dinesh** [IN/IN]; A-9/301, Rutu Enclave, Ghodbunder Road, Kavesar, Thane (West) 400 601, Maharashtra (IN). **KULKARNI, Sushrut** [IN/IN]; C002 Ganga Yamuna Apartments, Near Mohinder Singh School, Behind Ganesh Tower, Agra Road, Kalyan (W) 421 301 (IN). **SUKTHANKAR, Mangesh** [IN/IN]; Madgaonkar Building, Above Post Office, Court Lane Borivali (west), Mumbai-400 092, Maharashtra (IN). **THAKKER, Prashant** [IN/IN]; CTS 175, J-45 Mahandra Park, Narayan Nagar, L.B.S. marg,

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: VENLAFAXINE COMPOSITIONS COMPRISING PELLETS WITH DOUBLE LAYER COATING

(57) Abstract: This invention provides coated pellets comprising a) a pellet core which comprises venlafaxine hydrochloride; b) a first coating which comprises a lipophilic layer or a sparingly water-soluble layer, and c) a second coating which comprises a water-insoluble polymer or polymer mixture. In another aspect this invention provides compositions which comprises the coated pellets. In a further aspect, the invention provides a process for preparing the coated pellets which process avoids use of organic solvents at least for the second coating.



WO 2004/091580 A1

## VENLAFAXINE COMPOSITIONS COMPRISING PELLETS WITH DOUBLE LAYER COATING

This invention relates to pharmaceutical compositions of venlafaxine.

5

Venlafaxine is the non-proprietary name for 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol and is useful in treating a number of disorders including depression, anxiety, panic disorder and pain. Venlafaxine is administered as venlafaxine hydrochloride in treating depression. See The Merck Index, 12th Edition, entry 10079.

10

Published European patent application EP 797 991 A discloses encapsulated extended release formulations of venlafaxine hydrochloride which comprise a hard gelatin capsule containing spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropylmethylcellulose coated with ethyl cellulose and hydroxypropylmethylcellulose.

15 Solvents used in the coating step include methylene chloride and anhydrous methanol.

The present applicants have sought to overcome the drawbacks of hitherto known formulations of venlafaxine.

20 In one aspect, therefore, this invention provides coated core pellets comprising venlafaxine for use in a delayed and/or extended release formulation which core pellets undergo at least one coating step in the absence or substantial absence of organic solvents.

In another aspect, this invention provides a coated pellet comprising

- 25 a) a pellet core which comprises venlafaxine hydrochloride;
- b) a first coating which comprises a lipophilic layer or a sparingly water-soluble layer, and
- c) a second coating which comprises a water-soluble or water-insoluble polymer.

30

- 2 -

The pellet core may comprise in addition a carrier, for example microcrystalline cellulose. The pellet core may comprise in addition a binder, for example a cellulose derivative, e.g. hydroxypropylmethylcellulose (HPMC). The present applicants have found that HPMC of e.g. grade K 4 M has an appropriate viscosity for use in this invention.

5

The pellet core may be spheroidal in geometry and typically exhibits a diameter, when coated, of between around 0.5 mm to 2 mm, e.g. 0.7 to 1.75mm, for example 0.8 mm to 1.5 mm.

10 The first coating and second coating may each be complete or substantially complete, e.g. so as to provide a surface coverage of at least 60 %, e.g. 70 % or more, e.g. 80 to 95 % around the core (first coating) or around the first coating (second coating). Complete coatings are preferred.

15 The first coating may comprise between 0.5 to 5% by weight, e.g. 1 to 4%, of the first-coated pellet core.

The second coating may comprise 8 to 30% by weight, e.g. 10 to 25%, based on the total weight of the double-coated core.

20 The first coating serves to protect the pellet core from moisture, both in storage and in use.

The lipophilic layer may comprise a fat, fatty alcohol or wax. The lipophilic layer preferably comprises cetostearyl alcohol, castor oil or dibutyl phthalate.

25 The sparingly water-soluble layer may comprise a carbohydrate or a sugar, e.g. lactose, in the form of an aqueous suspension wherein the concentration of the carbohydrate or sugar is at least about 0.1 g/ml, e.g. 0.15 to 0.25 g/ml or greater, e.g. 0.28 g/ml to 0.4 g/ml or even higher, e.g. 0.41 to 0.6 g/ml, for example 0.43 or 0.5 g/ml.

30 The sparingly water-soluble layer, which may be formed by spray-coating, may comprise lactose in an amount of up to about 30% to 40% by weight.

The first coating may be free of, or substantially free of, ethyl cellulose.

The water-soluble or water-insoluble polymer may be selected from acrylate-based aqueous dispersions, ethylcellulose aqueous dispersions and polyvinyl acetate aqueous dispersions.

5 Thus the second coating is aqueous-based and serves to provide the extended release effect.

Water-insoluble polymers are preferred and may serve to control release of the venlafaxine. The water-insoluble polymer may display pH-independent solubility and may comprise a water-insoluble polymer mixture.

10 The term "water-insoluble", as used herein is understood to mean a polymer solubility in water at room temperature of less than 100 mg/litre, e.g. 20 mg/litre or less, e.g. 10mg/litre or less, e.g. 1mg/litre or less.

15 In a preferred aspect, the pellet core and/or coating(s) of this invention are free of, or substantially free of, polyvinylpyrrolidone.

In another aspect, this invention provides a composition comprising coated pellets as herein described. The composition may be in tablet, hard gelatine capsule or sachet form.

20 In another aspect, this invention provides a coated pellet consisting of or consisting essentially of

a) a core containing venlafaxine hydrochloride in an amount of between 30 and 60 % by weight, microcrystalline cellulose in an amount of between 40 and 65% by weight, and  
25 HPMC K 4 M in an amount of between 0.3 and 0.8% by weight, wherein the respective weights are in relation to the double-coated core;

b) a first coating containing cetostearyl alcohol in an amount of between 1.0 and 4.0 %, e.g. 1.7 and 3.5 %, by weight of the first-coated pellet core; and

- 4 -

- c) a second coating containing an acrylate-based polymer in an amount of between 9 and 25%, e.g. 9 and 13 %, by weight based on the total weight of the double-coated core, and talc in an amount of between 2 and 15%, e.g. 3 and 8 %, by weight based on the total weight of the double-coated pellet core.

5

Suitable acrylate-based polymers or water-insoluble polymers having pH-independent solubility are available commercially e.g. from the Röhm company, Germany, under the trade marks EUDRAGIT, SURELEASE or AQUACOAT, e.g. EUDRAGIT NE 30 D, EUDRAGIT RL 30 D, EUDRAGIT RS 30 D or KOLLCOAT SR as dry polymer.

10

The second coating may further comprise triethyl citrate or dibutyl phthalate, e.g. in an amount of 5 to 35%, e.g. 10 to 30 %, by weight of the dry polymer.

In a further aspect, this invention provides a composition consisting of or consisting essentially of coated pellets as herein described. The composition may be in tablet, hard gelatine capsule or sachet form.

In a further aspect, this invention provides a process for preparing pellets as herein described which comprises the steps of

20

Ai) forming a pellet core mixture comprising venlafaxine hydrochloride with water or an aqueous solution of a binder,

Aii) extruding and spheronising the mixture, and subsequently drying,

25

Aiii) applying the first coating,

Aiv) applying the second coating, and subsequently sieving so as to obtain coated pellets within the desired size range,

wherein the process is carried out in the absence or substantial absence of any organic solvent at least in the second layer.

Coating steps Aiii) and Aiv) may employ conventional fluidised bed processes. Alternatively, the first coating layer may be applied using a spray melt process or by using a tangential coating process.

5

In another embodiment, the first coating layer may be dissolved in an organic solvent medium, e.g. methylene chloride or methanol, and sprayed onto the pellet cores.

In a further aspect, this invention provides a process for preparing pellets as herein described which comprises the steps of

10

Bi) forming a pellet core mixture comprising venlafaxine hydrochloride, microcrystalline cellulose and HPMC with water or an aqueous solution of a binder,

15 Bii) extruding and spheronising the mixture, and subsequently drying,

Biii) collecting the core pellets between 0.8 mm to 1.75 mm for further processing,

Biv) applying the first coating, and

20

Bv) applying the second coating

wherein the process is carried out in the absence or substantial absence of any organic solvent at least in the second layer.

25 Coating steps Biv) and Bv) may employ conventional fluidised bed processes. Alternatively, the first coating layer may be applied using a spray melt process or by using a tangential coating process.

A preferred embodiment of each of the above processes is such that the process is carried out in the absence or substantial absence of any organic solvent in both the first coating layer and in the second coating layer.

30

- 6 -

The venlafaxine hydrochloride is sourced from the Medichem company, Spain. The venlafaxine may be used in any polymorphic form, e.g. in the forms known as Form I or Form II. The compositions of this invention may be administered to adults in doses ranging from 75 mg to 350 mg venlafaxine per day.

Following is a description by way of example only of compositions of this invention.

#### Example 1

Pellets according to the following composition are prepared and filled into hard gelatin capsules.

15	I	Core pellets	Quantity per capsule (mg)
		venlafaxine HCl	169.70
		microcrystalline cellulose	199.0
		HPMC K 4 M	1.85
20	II	Wax coating	
		cetostearyl alcohol	9.26
25	III	Polymer coating	
		Eudragit NE 30 D	56.97
		talc	28.49
		Total weight of coated pellets	476.90

The core pellets are prepared by mixing the above components with a small amount of water, i.e. enough to form a paste without dissolving the venlafaxine, under I followed by extrusion spheronisation. The wax coating is applied using a fluidised bed process at or close to the melting temperature of the coating layer. The subsequent polymer (sustained release) coat is

- 7 -

applied by a fluidised bed process. The resulting coated pellets are sieved so as to obtain a desired pellet size range of between 0.85 mm and 1.75 mm.

#### Example 2

- 5 Pellets are prepared in analogous manner to those in Example 1 with replacement of the wax coating by an aqueous suspension of lactose at a concentration of 0.15 g/ml. The suspension is sprayed onto the cores using a perforated pan or a fluidised bed process.

10 In view of the small amount of water involved in the first coating step, negligible dissolution of venlafaxine takes place and a protective layer is formed between the pellet core and the second coating.

#### Examples 3a) and 3b)

15 Pellets according to the following composition are prepared and filled into hard gelatin capsules.

20	I	Core pellets	Quantity per capsule (mg)
		venlafaxine HCl	169.70
		microcrystalline cellulose	193.27
		HPMC K 4 M	1.85
	II	Wax coating	-
		cetostearyl alcohol	10.03
25	III	Polymer coating	
		Eudragit NE 30 D	70.10
		talc	35.05
		Total weight of coated pellets	480.00

30



- 8 -

The core pellets are prepared by mixing the above components with a small amount of water, i.e. enough to form a paste without dissolving the venlafaxine, under I followed by extrusion spheronisation. The pellets with size between 0.8mm and 1.75mm are collected. The wax coating is applied using

- 5 in Example 3a) a fluidised bed process, and  
in Example 3b) tangential coater,  
at or close to the melting temperature of the coating layer. The subsequent polymer (sustained release) coat is applied by a fluidised bed process.

10 Examples 4a) and 4b)

Pellets are prepared in analogous manner to those in Example 1 with replacement of the wax coating by an aqueous suspension of lactose at a concentration of 0.43 g/ml. The suspension is sprayed onto the cores using

- 4a) a perforated pan, or  
15 4b) a fluidised bed process.

In view of the small amount of water involved in the first coating step, negligible dissolution of venlafaxine takes place and a protective first layer is formed between the pellet core and the second coating.

20

Example 5

A capsule composition is prepared in analogous manner to that in Example 1 with the following component amounts.

25	I	Core pellets	<u>Quantity in %</u>
		venlafaxine HCl	37.3 % by weight of core pellets
		microcrystalline cellulose	62.1 % by weight of core pellets
		HPMC K 4 M	0.5 % by weight of core pellets
30	II	Wax coating	
		cetostearyl alcohol	2.5 % by weight of core pellets

- 9 -

## III Polymer coating

Eudragit NE 30 D (dry) 15% by weight of pellets with first coating  
 talc 50% by weight of dry polymer

5

The following dissolution profiles are observed using USP Apparatus 1 at 100 rpm in purified water at 37°C.

Cumulative amount dissolved (%)				
Time	EFFEXOR ER	Formulation of	Dissolution range	
(hours)		Example 3	in %	
2	14	8	< 30	
4	40	32	30 to 55	
15 8	67	68	56 to 80	
12	79	85	65 to 90	
24	93	98	> 80	

20 The principal advantages of the pellets and compositions of the present invention include a release profile of venlafaxine as effective as the commercially available product, however without the use of an organic solvent medium at least for application of the second coating. A further advantage is the absence of any organic solvent residue in the coated pellets.

25 The process is more cost-effective and less hazardous than hitherto known processes.

The coated pellets of this invention are thus produced using more economically and environmentally attractive processes than hitherto known processes for venlafaxine.

30

Claims

1. A coated pellet comprising
  - a) a pellet core which comprises venlafaxine hydrochloride;
  - 5 b) a first coating which comprises a lipophilic layer or a sparingly water-soluble layer, and
  - c) a second coating which comprises a water-insoluble polymer or polymer mixture.
2. A pellet as claimed in claim 1 wherein the core additionally comprises a carrier, e.g. microcrystalline cellulose.
- 10 3. A pellet as claimed in claim 1 or claim 2 wherein the core further comprises a binder.
4. A pellet as claimed in claim 3 wherein the binder comprises a cellulose derivative.
- 15 5. A pellet as claimed in claim 3 or claim 4 wherein the binder comprises hydroxypropyl methylcellulose (HPMC).
6. A pellet as claimed in claim 1 or claim 2 wherein the lipophilic layer comprises a fat, fatty alcohol or wax.
- 20 7. A pellet as claimed in any preceding claim wherein the lipophilic layer comprises cetostearyl alcohol, castor oil or dibutyl phthalate.
8. A pellet as claimed in claim 1 or claim 2 wherein the sparingly water-soluble layer  
25 comprises a sugar, e.g. lactose, in the form of an aqueous suspension wherein the concentration of the sugar is at least 0.3 g/ml.
9. A pellet as claimed in any preceding claim wherein the water-insoluble polymer is  
30 selected from polymethacrylate dispersions, ethylcellulose dispersions and polyvinyl acetate dispersions.

10. A composition comprising pellets as claimed in any preceding claim.
11. A composition as claimed in claim 10 in tablet, hard gelatine capsule or sachet form.
- 5 12. A process for preparing coated pellet cores which process comprises the steps of
- i) forming a pellet core mixture comprising venlafaxine hydrochloride with water or an aqueous solution of a binder,
  - 10 ii) extruding and spheronising the mixture, drying and sieving,
  - iii) applying a first coating, and
  - iv) applying a second coating,
- 15 wherein the process is carried out in the absence or substantial absence of any organic solvent medium at least in the second coating.
13. A process as claimed in claim 12 wherein the pellet core mixture further comprises
- 20 microcrystalline cellulose and HPMC.
14. A process as claimed in claim 12 or claim 13 wherein the process is carried out in the absence or substantial absence of any organic solvent medium in both the first and second coatings.
- 25 15. A coated pellet produced by the process as claimed in any one of claims 12 to 14.
16. A coated pellet consisting of or consisting essentially of
- a) a core containing venlafaxine hydrochloride in an amount of between 30 and 60 % by
  - 30 weight, microcrystalline cellulose in an amount of between 40 and 65% by weight, and

- 12 -

HPMC K 4 M in an amount of between 0.3 and 0.8% by weight, wherein the respective weights are in relation to the double-coated core;

b) a first coating containing cetostearyl alcohol in an amount of between 1.7 and 3.5 % by weight of the first-coated pellet core; and

c) a second coating containing an acrylate-based polymer in an amount of between 9 and 13% by weight based on the total weight of the double-coated core, and talc in an amount of between 3 and 8% by weight based on the total weight of the double-coated pellet core.

17. A composition comprising pellets as claimed in claim 16.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/003255

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/16 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 797 991 A (AMERICAN HOME PROD) 1 October 1997 (1997-10-01) cited in the application the whole document	1-17
A	WO 99/22724 A (AMERICAN HOME PROD) 14 May 1999 (1999-05-14) the whole document	1-17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## ° Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

2 September 2004

Date of mailing of the international search report

14/09/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Villa Riva, A

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/003255

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0797991	A	01-10-1997	AT 257011 T	15-01-2004
			AU 727653 B2	21-12-2000
			AU 1640097 A	02-10-1997
			BR 9701304 A	29-09-1998
			CA 2199778 A1	25-09-1997
			CN 1403077 A	19-03-2003
			CN 1164389 A , B	12-11-1997
			CZ 9700772 A3	12-11-1997
			DE 69727000 D1	05-02-2004
			DE 69727000 T2	09-06-2004
			DK 797991 T3	05-04-2004
			EP 1331003 A1	30-07-2003
			EP 0797991 A1	01-10-1997
			ES 2210454 T3	01-07-2004
			HU 9700589 A2	29-09-1997
			IL 120382 A	24-06-2003
			IN 187337 A1	30-03-2002
			JP 10007552 A	13-01-1998
			NO 971206 A	26-09-1997
			NZ 314442 A	29-06-1999
			PL 318954 A1	29-09-1997
			RU 2176912 C2	20-12-2001
			SI 797991 T1	30-04-2004
			SK 30197 A3	08-10-1997
			TR 9700190 A2	21-10-1997
			TW 493993 B	11-07-2002
			US 2002197307 A1	26-12-2002
			US 2003215507 A1	20-11-2003
			US 6274171 B1	14-08-2001
			US 2001055612 A1	27-12-2001
			US 2002025339 A1	28-02-2002
			ZA 9702403 A	21-09-1998
WO 9922724	A	14-05-1999	AT 237320 T	15-05-2003
			AU 747978 B2	30-05-2002
			AU 1300399 A	24-05-1999
			BG 104397 A	28-02-2001
			BR 9813179 A	22-08-2000
			CA 2305242 A1	14-05-1999
			CN 1278165 T	27-12-2000
			CZ 20001659 A3	17-10-2001
			DE 69813602 D1	22-05-2003
			DE 69813602 T2	06-11-2003
			DK 1028718 T3	28-07-2003
			EE 200000212 A	16-04-2001
			EP 1028718 A2	23-08-2000
			ES 2196620 T3	16-12-2003
			HK 1029056 A1	21-11-2003
			HR 20000213 A1	31-12-2000
			HU 0004287 A2	29-04-2002
			ID 26317 A	14-12-2000
			JP 2001521892 T	13-11-2001
			MA 24691 A1	01-07-1999
			NO 20002126 A	04-05-2000
			NZ 504460 A	31-01-2003
			PL 341141 A1	26-03-2001
			PT 1028718 T	31-07-2003
			SI 1028718 T1	31-08-2003

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP2004/003255

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9922724	A	SK 6472000 A3	07-11-2000
		TR 200001232 T2	21-12-2000
		TW 555568 B	01-10-2003
		WO 9922724 A2	14-05-1999
		US 2002197307 A1	26-12-2002
		US 2003215507 A1	20-11-2003
		US 6274171 B1	14-08-2001
		US 2001055612 A1	27-12-2001
		US 2002025339 A1	28-02-2002
		ZA 9810081 A	04-05-2000